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EXAMINER	
KIM, ALEXANDER D	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,455	KRETSCHMAR ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/26/2006,12/18/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. By virtue of a preliminary amendment filed on 09/26/2006, claim 21 is canceled; and claims 1-20 and 22-23 are amended. Thus, claims 1-20 and 22-23 are pending in this instant case.

Information Disclosure Statement

2. The information disclosure statements (IDS) filed on 09/26/2006 and 12/18/2009 has been reviewed, and its references have been considered. A copy of Form PTO/SB/08 is attached to the instant Office action.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: foreign priority information is missing.

Appropriate correction is required.

Claim Objections

4. Claims 1-20 and 22-23 are objected to because of the following informalities:

(a) Claim 1 (Claims 5-20 and 22-23 dependent therefrom) recites "the step of". It should be ---a step of--- to improve the format of claim.

(b) Claims 1, 2, and 22 (Claims 3-20 and 23 dependent therefrom) recites "VWF". The use of abbreviation, unless otherwise obvious and/or commonly used in the art, *e.g.,* "DNA", should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used in its first appearance in the claims.

(c) Claim 2 (Claims 3-4 dependent therefrom) recites "The process for purifying VWF comprising the steps of...". Since Claim 2 is independent claim, it should be ---A process for purifying VWF comprising steps of ...--- to improve the format of claim.

(d) Claims 3 and 13 recites "VWF is found in the flow" (emphasis added). It should be ---a flow--- to improve the format of claim. Also, the term "a flow" has not been defined by the instant specification. If it is applicants' intention of using the term "flow" is to indicate a solution which has been passed though the hydroxylapatite matrix, the appropriate term would be "flow-through" or "flow through" which is the art recognized terminology.

(e) Claims 22 and 23 is objected to because of recitation of "A VWF containing composition... " and "A composition ..." in Claims 22-23, respectively. The examiner suggest reciting ---A composition comprising a VWF obtained by...--- in Claim 22; and ---The composition according to claim 22, wherein the VWF is a purified VWF--- in Claim 23, to improve format of claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 5-20 and 22-23 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 1 (Claims 5-20 and 22-23 dependent therefrom) recites "the step of carrying out at lest one hydroxylapatite flow chromatography", wherein the term "the step" lacks antecedent basis. It is noted that the instant specification recites, on bottom of page 4 to top of page 5, "The process according to the invention comprises that (i) a composition containing VWF and one or more contaminating proteins is contacted with a hydroxylapatite matrix so as to bind at least one contaminating protein to the hydroxylapatite matrix while VWF is not substantially bound to the hydroxylapatite matrix, and optionally thereafter (ii) unbound VWF is separated from the hydroxylapatite matrix. This embodiment is referred to as "flow chromatography" in the present application." Thus, Claim 1 (Claims 5-23 dependent therefrom) encompasses said steps of (i) and (ii) as set forth above. However, it is unclear if "the step" refers to said specific steps as noted in the

specification and if that is the intention of the applicants, the Examiner suggest to recite said steps in Claim 1.

(b) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 5 recites the broad recitation "pH of 6.5 to 8.0", and the claim also recites "preferably 6.8 to 7.5" which is the narrower statement of the range/limitation.

(c) Claim 6 recites "the running buffer". There is insufficient antecedent basis for this limitation in the claim because a running buffer is not recited in Claim 1, nor defined in the instant specification. Is "the running buffer" the buffer used in one of the instant example? It is unclear which buffer is encompassed by "the running buffer".

Appropriate correction and/or clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-20 and 22-23 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a process of purifying VWF by contacting composition containing VWF with any contaminant protein(s) with a hydroroxylapatite matrix and separating bound or unbound VWF from the hydroroxylapatite matrix. The recited term "VWF" encompasses any VWF (unlimited structural limitations without any functional requirement) regardless of its source (e.g., a wild-type VWF found in its source organism as well as VWF produced by the recombinant host cell as supported by the instant Claim 19); wherein a recombinant VWF encompasses any VWF having "one or more amino acids may be substituted, deleted and/or added. The variants usually have VWF activity" (see page 11, lines 5-7); thus, instant VWF does not excludes any structural variants including the one without VWF activity (any fragment of VWF, for example) in light of instant specification.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

The instant specification teach a process of purifying a wild-type VWF or any previously known VWF in the art by passing through a hydroxylapatite chromatograph under bound and unbound conditions. However, the breadth of claim includes a genus method of purifying any VWF (unlimited structural limitations without any functional requirement) regardless of its source (e.g., a wild-type VWF found in its source organism as well as VWF produced by the recombinant host cell as supported by the instant Claim 19); wherein a recombinant VWF encompasses any VWF having "one or more amino acids substituted, deleted and/or added. The prior art and instant

specification teaches a method for purifying previously known human wild-type VWF having a known amino acid sequences and having the VWF coagulation activity (or a large enough fragment that known to bind to a hydroxylapatite matrix) using a hydroxylapatite column as disclosed below by Gorman et al. (Thrombosis Research, 1978, Vol. 12, pages 341-352, as cited in IDS), Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) and Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334). To fully describe a genus of mutant recombinant nucleic acid molecules, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these. However, the prior art and the instant specification do not describe method of any VWF including a variant thereof having any deletion, substitution and/or addition in amino acid sequences of said any VWF; thus, the instant specification and prior art do not describe a sufficient structure (e.g., any variant of VWF) and function (e.g., a blood coagulation activity and/or binding function to a hydroxylapatite) relationship of species of VWF for purifying it with hydroxylapatite matrix because there is no disclosure of correlation between function and structure for said genus method. Thus, the instant specification and the prior art cannot describe the structure of a very broad claimed genus method of purifying very broad VWF and one

skilled in the art would not be in possession of the claimed genus by the instant specification.

7. Claims 1-20 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a process for purifying a VWF with previously known amino acid sequences through hydroxylapatite matrix, **does not** reasonably provide enablement for a process method for purifying any VWF, which includes, but not limited to, any VWF having one or more amino acids are substituted, deleted and/or added with or without any activity such as any fragment (for example) of VWF from any source (native and recombinant), through hydroxylapatite matrix.

The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use of the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single,

simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The nature of the invention is drawn to a process of purifying a wild-type VWF or any previously known VWF in the art by passing through a hydroxylapatite chromatograph under bound and unbound conditions. However, the breadth of claim includes a genus method of purifying any VWF (unlimited structural limitations without any functional requirement) regardless of its source (e.g., a wild-type VWF found in its source organism as well as VWF produced by the recombinant host cell as supported by the instant Claim 19); wherein a recombinant VWF encompasses any VWF having one or more amino acids substituted, deleted and/or added. Applicants and the prior art teach a method for purifying a known human wild-type VWF with previously known amino acid sequence having the VWF coagulation activity (or a large enough fragment that known to bind to a hydroxylapatite matrix) using a hydroxylapatite column as disclosed below by Gorman et al. (Thrombosis Research, 1978, Vol. 12, pages 341-352, as cited in IDS), Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) and Dumas et al. (The Journal of Biological Chemistry, May 28,

2004, Vol. 279, pages 23327-23334). However, applicants disclose no direction or guidance on how to make and use the claimed process of purifying said any VWF using hydroxylapatite matrix wherein said any VWF has unlimited structure and does not require any function. Thus, the specification and prior art fail to describe sufficiently how to make and use the claimed genus process. Also, it is unpredictable for any VWR variants (any variants and/or fragments with unlimited structure, for example) to be used in purification by the claimed process and/or to be used in a composition (e.g., therapeutic composition) that requires the function of wild-type VWF, for example. Thus, it is unpredictable for any VWF variant encompassed by the claimed process for one skilled in the art to make and use the full scope of claims for purifying VWF. The said unpredictability makes the relative skill required in the art very high. For all of the above reason, it would require undue experimentation necessary for a method of using said any VWF variants which includes, but not limited to, a non functional VWF variants.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 5-11, 12, 14 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Gorman et al. (Thrombosis Research, 1978, Vol. 12, pages 341-352, as cited in IDS).

Gorman et al. teach a process of purifying VWF by hydroxylapatite (HA) chromatography. The process of Gorman et al. comprises: precipitation from plasma, gel filtration on Sepharoase 6B and HA wherein HA chromatography involves loading, washing with 5mM phosphate (pH 6.8), 0.1 M NaCl ; and eluting by 0.1 M phosphate (pH 6.8), 0.1 M NaCl from the gradient of 5 mM to 500 mM potassium phosphate buffer (e.g., washing and/or eluting) which resulted in co-elution having "Factor VIII coagulant activity, factor VIII related antigen and von Willebrand factor activity" (see the Abstract and the purification procedure on page 342, bottom); thus, the process of Gorman et al. and the co-eluted VWF product thereof meet the limitations of Claims 1-3, 5-11, 12, 14 and 22-23.

9. Claims 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS).

The factors to be considered for a product-by-process are summarized in MPEP 2113. “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” See In

re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983) and Ex parte Gray, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989).

Burnouf-Radosevich et al. teach a highly purified von Willebrand factor (vWF) in a purification buffer having very high specific activity (CBA) of 345 U/mg by the purification scheme disclosed in Table 1 (see page 4), which is shown to be a single band in the SDS-PAGE as shown in Fig. 3 on page 6; wherein the highly purified VWF by Burnouf-Radosevich et al. is obvious and/or same as the VWF composition encompassed by instant Claims 22-23 which is produced by method of Claim 1. Furthermore, a highly pure VWF composition prepared by Burnouf-Radosevich et al. which would not be changed by any additional purification step(s) such as HA chromatography since it is already in a pure form.

10. Claims 1-3, 5-12 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334).

As noted above, Claims 1-3, 5-12 and 22-23 encompasses a process of purifying von Willebrand Factor (VWF) or the purified VWF product thereof without any functional limitation, wherein a step comprising contacting a composition containing VWF and one or more contaminating proteins with a hydroxyapatite matrix, wherein said VWF encompasses native VWF as well as recombinant VWF in view of instant Claim 19,

which includes "variants having an amino acid sequence modified with respect to a wild-type VWF, wherein one or more amino acids may be substituted, deleted and/or added" in light of instant specification lines 4-13 on page 11. Thus, the solution containing wild type A1 domain of VWF (i.e., referred to as the A1) expressed in E. coli by Dumas et al. (see bottom left column, page 23328) meets the limitation of a composition containing VWF in Claim **1**.

Dumas et al. teach a process of loading wild type A1 domain of VWF (i.e., referred to as the A1) containing fraction onto hydroxyapatite (HA) column and eluted the A1 by a linear gradient from 20 mM HEPES, pH 8.0 to 20 mM HEPES, 0.5 M sodium phosphate monobasic, 0.5 M sodium phosphate dibasic, pH 6.6; and also teach "purified A1 was judged to be pure (>95%) by SDS-PAGE" which indicating there are about 5% contamination; see page 23328, right column, lines 9-14. Thus, the process of Dumas et al. meets all limitation of **Claims 1-3, 5-6 and 22-23**.

Because the HA chromatography process by Dumas et al. was performed in a separate step from previous chromatography steps as set forth in the purification method of Dumas et al., the process of HA chromatography by Dumas et al. meets the limitation of **Claims 7 and 12**. The step of washing out impurities in Claim 8 is inherently taught by the step of loading the A1 sample to the HA column and/or by the step of running a gradient as set forth above. Also, since the linear gradient by Dumas et al. teach contiguous gradient of 0 to 1000 mM phosphate ions (with sodium/potassium counter ions) and the binding, washing and eluting the VWF protein is performed by the loading (which encompasses binding and/or washing) and the

gradient (which encompasses washing and/or eluting) in the purification process by Dumas et al. Thus, the process of loading the sample and running said gradient on VWF sample by HA column chromatography taught by Dumas et al. meets all limitations of **Claims 8-11**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 1-17, 19 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) or Newman et al. (US Patent 5,710,254, Jan 20, 1998) in view of Labrou (Journal of Chromatography B, 2003, Vol. 790, pages 67-78), Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334), and Zardi et al. (Eur. J. Biochem., 1985, Vol. 146, pages 571-579).

Burnouf-Radosevich et al. teach a process of purification of VWF having following steps: cryoprecipitation of plasma by aluminum hydroxide at a certain pH (an example of a pH precipitation as well as cryoprecipitation), see "Starting Material" on page 2, middle of right column (meeting the limitation of Claims 14-18); and processing steps as shown in Table 1, on page 4; wherein impurities of purified VWF composition contains "traces of fibrinogen ... and fibronectin" in a highly sensitive immunoblotting

assay using specific polyclonal antibodies (see last three lines on page 5, right column; meeting the limitations of contaminant protein of Claims 3-4). Burnouf-Radosevich et al. further teach the drawback to using size exclusion chromatography has low protein resolution and lack of stability possible due to protease contamination (see bottom, left column, page 2); thus, affinity column is preferred. Newman et al. also teach "purification of von willebrand factor by affinity chromatography" (see the Title) according to methods disclosed through out the patent; and also teach the presence of "other coagulation factors and other plasma proteins, particularly fibronectin and fibrinogen" is deleterious to the health of the patient (see §, lines 42-46).

Burnouf-Radosevich et al. or Newman et al. **do not** teach a purification method using the hydroxylapatite matrix using Na+ and/or K+ phosphate in a purification buffer.

The use of hydroxylapatite column and the use of Na+ and/or K+ phosphate in a purification buffer (or gradient) for purifying a protein is well known at the time of instant invention as exemplified by the teachings of Labrou, Dumas et al., and Zardi et al. as explained herein.

Labrou teaches a hydroxyapatite is one of "unique in achieving the high standards of product purity dictated by the regulatory authorities for commercial bio products and a highly selective separation technique commonly used for the isolation and purification of biological macromolecules (see left column, lines 24-35, on page 68). Dumas et al. teach the purification of VWF domains using a hydroxyapatite column and appropriate buffer as set forth above. Zardi et al. also teach the hydroxyapatite chromatography column is useful in resolving and eluting a fibronectin and its domains.

Also, the recombinant VWF "biosynthesis in a cell and secretion" is well known by one skilled in the art as disclosed by Newman et al. (US Patent 5,710,254; see § lines 53-60).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the process of purifying VWF by Burnouf-Radosevich et al. by adding a hydroxyapatite chromatography step within the purification process by Burnouf-Radosevich et al. with a reasonable expectation of success because use of any combination of affinity column is well known in the purification of biomolecules which improve a purity or quality in final product of protein of interest (e.g., VWFs). The motivation to do so is provided by Burnouf-Radosevich et al. who teach the usefulness of highly purified VWF for clinical use for treatment of vWF patients (see end of the Abstract). In case VWF is eluded from the HA column, thee VWF can be said to be in a state such that VWF does not bind to the hydroxylapatite as written in Claim 13, and the purification procedure disclosed above would meet the limitation of "the flow fraction is re-chromatographed under binding conditions and the VWF fraction is eluted as noted in Claim 13 as long as the hydroxylapatite step is not the last column in the purification step. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

12. Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) or Newman et al. (US Patent 5,710,254, Jan 20, 1998) in view of Labrou (Journal

of Chromatography B, 2003, Vol. 790, pages 67-78), Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334), and Zardi et al. (Eur. J. Biochem., 1985, Vol. 146, pages 571-579) as applied to claims 1-19 and 22-23 above, and **further in view of** Winkelman (US Patent 4,789,733, Dec. 6, 1988, as cited in the IDS) and Ichitsuka et al. (US Patent 5,441,635, Aug. 15, 1995).

The teachings of Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., and Zardi et al. is disclosed as set forth above. As noted above, Burnouf-Radosevich et al. teach a process of purification of VWF which contains "traces of fibrinogen ... and fibronectin" (see last three lines on page 5, right column).

Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., and Zardi et al. **do not** teach a process of an acidic precipitation (i.e., lowering a pH of buffer, an example of recited "a pH precipitation" in Claim 18) prior to hydroxylapatite chromatography (or fluoroapatite chromatography).

Winkelman et al. discloses that blood plasma fractionation by lowering a pH from 7.0 to 6.0 increase the precipitation of fibronectin and fibrinogen (see §5, lines 60-65).

Ichitsuka et al. disclose the packing material (i.e., fluoroapatite) for liquid chromatography; wherein the fluoroapatite have superior to acid resistance compared to hydroxyapatite (see Example 7, §15, lines 51-52); "proved capable of obtaining a separation pattern similar to that of hydroxyapatite" (see §16, lines 1-2) and "can be used advantageously for separation and purification of proteins, enzymes..." (see Example 8, §16, lines 36-38).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the process of purifying VWF by Burnouf-Radosevich et al. by treating an acidic precipitation of VWF containing loading sample prior to loading to a fluoroapatite column instead of hydroxyapatite with a reasonable expectation of success because said acidic precipitation process and using a fluoroapatite column instead of hydroxyapatite can be easily performed by one skilled in the art. The motivation to perform an acidic precipitation is provided by Winkelman et al. who teach the usefulness of an acidic precipitation further removes contaminants of fibronectin and/or fibrinogen in the process of VWF purification disclosed by Burnouf-Radosevich et al. because it is advantageous for preparing a higher quality (i.e., higher purity) therapeutic agent; and the motivation to use a fluoroapatite column instead of hydroxyapatite is provided by Ichitsuka et al. who teach a fluoroapatite column has superior stability in an acidic condition which would be created by the precipitation as noted above. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

13. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) or Newman et al. (US Patent 5,710,254, Jan 20, 1998) in view of Labrou (Journal of Chromatography B, 2003, Vol. 790, pages 67-78), Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334), and Zardi et al. (Eur. J. Biochem., 1985, Vol. 146, pages 571-579) Winkelman (US Patent 4,789,733,

Dec. 6, 1988, as cited in the IDS) and Ichitsuka et al. (US Patent 5,441,635, Aug. 15, 1995) as applied to claims 1-20 and 22-23 above, and **further in view of** Daniel Marshak (1996, Cold Spring Harbor Laboratory Press, Strategies for Protein Purification and Characterization: A Laboratory Course Manual) and Schroder et al. (Analytical Biochemistry, 2003, Vol. 313, pages 176-178).

As noted above, Claim 13 encompasses a method step of re-chromatographing the VWF fraction using hydroxylapatite or any other chromatograph resin as a second binding step. The instant rejection is focused in case the same hydroxylapatite is used twice.

The teachings of Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., Zardi et al. Winkelman and Ichitsuka et al. is disclosed as set forth above.

Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., Zardi et al. Winkelman and Ichitsuka et al. **do not** teach a process of running VWR fraction on a hydroxylapatite chromatograph under non-binding conditions and re-chromatograph said VWR fraction on a hydroxylapatite again second time.

Daniel Marshak teaches "It is not uncommon to see published protocol that calls for two or three successive DEAE-cellulose columns" and "It is not bad to use two anion- or cation-exchange steps at very different pH" (see page 58, lines 29-31 and lines 37-38).

Schroder et al. teach the hydroxyapatite "involves both anionic and cationic exchange" (see right column, lines 11-12) and "the phosphate concentration required to

elute any protein can be reduced by raising the pH" (emphasis added; i.e., binding is weaker at higher pH; see right column, lines 24-25).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the process of purifying VWF by incorporating a step of using hydroxylapatite multiple times wherein the VWF would be present in the flow-through in one time and the VWF would be bound to hydroxylapatite and eluted by the phosphate ions by adjusting or optimizing the pH of buffer and loading sample because manipulation and/or optimization of a column chromatography protein purification scheme is readily performed by one skilled in the art. The motivation to do so is well known by one skilled in the art who has desired to obtain more pure VWF final product which is advantageous for preparing a higher quality (i.e., higher purity) therapeutic VWF agent. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-6, 8-17 and 26-27 of U.S. Patent No: to be issued, from the US Patent Application 10/594,454, wherein the applicants have paid issue fee on 12/18/2009). Although the conflicting claims are not identical, they are not patentably distinct from each other because for the reasons set forth below: Claims 4, 6, 9, 10, 26 and 27 of issued claims from the US Patent Application 10/594,454 anticipates instant Claims **1-2, 6, 8 and 10-11**. The process of instant Claims **7 and 13** is obvious from Claims 4, 6, 9, 10, 26 and 27 of issued claims from the US Patent Application 10/594,454 in view of the specification of US Patent Application 10/594,454, page 6, lines 20-23, which disclose loading VWF which is not bound to a first hydroxylapatite to the second hydroxylapatite matrix in binding conditions. The process of Claim **9** is obvious from Claims 4, 6, 9, 10, 26 and 27 of issued claims from the US Patent Application 10/594,454 in view of the specification of US Patent Application 10/594,454, page 5, lines 5-10, which disclose a solution containing VWF having 0 to 200 mM, preferably 1 to 100 mM, more preferably 1 to 50 mM, most preferably 10 to 30 mM sodium and/or potassium phosphate in a binding step. Claim 4 in view of its dependent Claim 8 of issued claims from the US Patent Application 10/594,454

anticipates instant Claims **3-4**. Claim 5 issued claims from the US Patent Application 10/594,454 anticipates instant Claims **5 and 12**. Claims 11-17 of issued claims from the US Patent Application 10/594,454 anticipate instant Claim **14-20,** respectively.

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
>
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
>
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-18 are provisionally rejected on the ground of nonstatutory double patenting over claims 2, 4-15, 17 and 24 of U. S. Patent Application No. 10/594,453 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the US patent application and the application are claiming common subject matter, as follows: Instant claims 1-18 are anticipated and/or obvious by Claims 2, 4-15, 17 and 24 from US Patent Application No. 10/594,453 [i.e., species of instant claimed process by

further limiting limitation(s); wherein Claim 17 specifically recites the coagulation factor is **von Willebrand factor** which is encompassed by its independent claim 2 (i.e., having a pH precipitation as shown by the instant Claim 18) and all of its dependent claims 4-6, 8-15, 17 and 24], in view of the specification of US Patent Application No. 10/594,453 as explained below. It is noted that the certified translation of foreign priority application is the specification in US Patent application 10/594,**454**; and another related application 10/594,453 do not have specification filed in the application. Thus, for the examination purpose, the certified translation of foreign priority application in US Patent application 10/594,453 is treated as the specification (although it was filed and labeled as FRPR, see FRPR filed on 9/26/2006 having 18 pages). The specification of US Patent Application No. 10/594,453 discloses separating unbound VWF from hydroxyapatite while fibronectin is bound to hydroxyapatite (see page 7, top; instant Claims 3-4); discloses carrying out hydroxyapatite chromatography at pH 7.0-7.5 (for example, see page 7, line 17, instant claims 5 and 12); discloses the process of instant Claims 6 and 8-11 (see bottom of page 8 to top of page 9); discloses the process of instant Claims 7 and 13 (see bottom of page 10 to top of page 11); discloses the process of instant Claims 14-17 (see page 4, lines 1-4).

More specifically, the process of Claims 4-5 and 9 of US Patent Application No. 10/594,453 anticipate instant Claim 9. The process of Claims 14-15 of US Patent Application No. 10/594,453 anticipate instant Claims 15-17.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656